# Pathology of Early Malignant Change in the Ovary: A short review article

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**Abstract**

*Diagnosis of early malignant change in ovarian tumor is very important for initiation of treatment and plans other strategies for this tumor. Our knowledge of the pathology of early malignant change in the ovary is reviewed. The concept of ovarian intraepithelial neoplasia is discussed, and the malignant potential of ovarian cystadenomas is considered. The question of overt malignant change in tumors of borderline malignancy is also reviewed. It is concluded that any advance in our understanding and our knowledge of the early stages of malignant change in the ovary will only come from the use of newer techniques that allow a more sophisticated approach than that allowed by purely morphological methods and will lead to define better atrategies and treatment plan for this aggressive tumor.*

***Key Words:*** *Ovarian tumor-Early malignant change.*

## Introduction

Ovarian epithelial cancer affects over 26,000 American women annually, and it accounts for approximately 5% of all cancers exclusive of cutaneous epithelial malignancies and many in situ carcinomas except bladder[1]. The term ovarian cancer applies in general to malignant tumors arising from the modified peritoneal mesothelium that covers the surface of the ovary[2]. These epithelial ovarian cancers (EOC) make up 90% of all human ovarian malignant tumors and display a wide range of histologic features, usually recapitulating the morphology of endocervix, endometrium, or Fallopian tubes that are embriologically related to surface epithelium[3,4]. Clinical discovery of ovarian surface epithelial cancer is often late[5]. Ovarian cancer is most prevalent cause of death from a gynecologic malignancy in the Western World, primarily reflecting the fact that it produce vague symptoms, resulting in diagnosis at an advanced stage[6]. In contrast to breast cancer, where most cases are detected at an early stage, only 25% of ovarian cancer diagnosed at stage I, when the cure rate is almost 90%. The cure rate for ovarian cancer diagnosed at an advanced stage is less than 20%[7]. Ovarian cancer mortality has not significantly decreased due to our poor understanding of the underlying biology and natural history[8].

## Genetics of ovarian cancer:

It is well known that ovarian cancer has a large number of genetic changes involving both activation of oncogenes and loss of tumor-suppressor genes[9], thus complicating determination of the importance of an individual gene's alteration. Even though numerous genes with altered expression in epithelial ovarian cancer are under investigation worldwide, only few are likely to be casual and will provide new targets for diagnosis and therapy of this malignancy[10,11]. Ovarian cancer has been referred to as very complex and hetrogenous. Because of this, tumors with the same histologic features that arise in different patients may display diverse alterations with different patterns of oncogene activation or tumor-suppressor gene loss[7].

## Discussion

What is meant by the term "early"? Gynecologists usually regard a small Stage IA ovarian adenocarcinoma as being an early lesion, but this view betrays a lack of adequate awareness of tumor cell kinetics. Remarkably few data are available about the cellular dynamics of ovarian neoplasia; however, in the gastrointestinal tract it has been estimated that progression from a single cell that has undergone malignant change (accepting the monoclonal hypothesis of malignancy) to a tumor that is several millimeters in diameter takes between 2 and 6 years, whilst the evolution of a clinically detectable lesion may take as long as 14 years (12). Progression from a clinically detectable neoplasm to death can, by contrast, take as short a time as 2 years. Any tumor that can be seen with the naked eye, even one only I cm in diameter, is therefore not an early lesion as such but an "early late" lesion-and one that certainly has a potential not only for metastatic spread but for leading to the death of the patient.

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**Further, what is meant by the term "malignant"?**

Transformation of a cell from "normal" to "malignant" is not a one-stage process but is characterized by a series of changes in the genetic apparatus of the cell. Where exactly in this chain of events a cell becomes "malignant" rather than "nonmalignant" is currently an unresolved question that can not be resolved in terms of morphology. It could, however, be claimed, with some justification, that acquirement of the ability to invade is clear evidence of malignancy; acceptance of this view would exclude intraepithelial neoplasia and tumors of borderline malignancy from the category of "'malignant" and would, unfortunately, lead to normal trophoblast being regarded as a malignant" tissue.

It is clear that it is difficult to define, let alone discuss, the pathology of early malignant change in the ovary. Nevertheless, there are recognized histological abnormalities in the ovary that are thought to be indicative of a high risk of progression to a frankly malignant neoplasm. Thus, overgrowth of germ cells in a gonadoblastoma is clearly seen to be a precursor of a dysgerminoma, even though the cells are still within the confines of the original "islands" of the benign lesion. Similarly, the presence of intraepithelial neoplasia in squamous epithelium within a mature cystic teratoma is thought to be the starting point of a squamous cell carcinoma, and granulosa cell proliferation in the cellular islands of a sex cord tumor with annular tubules is regarded as a precursor of granulosa cell tumor.

These examples refer, however, to relatively rare neoplasms; of more importance is the recognition of the early stages of a malignant epithelial neoplasm of the ovary. Clearly, an ovarian adenocarcinoma can arise de novo in an otherwise normal ovary, may originate from a benign tumor, or can evolve from a neoplasm of borderline malignancy. In the normal ovary, it is widely thought that the first stage in the evolution of an epithelial neoplasm, particularly one of serous type, is commonly an invagination of the surface epithelium of the ovary into the underlying cortical stroma to form an inclusion cyst; malignant change subsequently occurs within the cyst[13,14]. Inclusion cysts are seen with considerable frequency in the ovary; however, in most pathologists' experience, detection of atypia within the lining cells of inclusion cysts is extremely rare. Certainly, there has been no systematic documentation of "in-situ" neoplastic change within such cysts.

Carcinomas could, of course, arise directly from the surface epithelium of the ovary, and changes thought to indicate neoplastic change in this epithelium have been described in recent years, to the extent that a condition of "ovarian intraepithelial neoplasia" has been defined. This histological abnormality was first recognised in a study of three pairs of identical twins, one of each pair having an ovarian adenocarcinoma. The other sister in each pair underwent prophylactic oophorectomy, and "dysplastic" abnormalities were noted in the surface epithelium of the ovaries in each case[15]. Subsequently, nuclear pleomorphism, irregular distribution_of nuclear chromatin, stratification, and loss of nuclear polarity have been described as characteristic feature of ovarian intraepithelial neoplasia, based on the findings in the surface epithelium adjacent to ovarian adenocarcinomas as opposed to the appearance of the surface epithelium in ovaries free of neoplastic disease[16,17]. Whether, in fact, the abnormalities described as "ovarian intraepithelial neoplasia" truly represent a preinvasive neoplastic lesion (and, if so, the magnitude of its potential for progression to invasive neoplasia) will probably never be determined. Currently, the diagnosis of this abnormality is made only in oophorectomy specimens, and although it has been suggested that prospective follow-up of high-risk patients in whom this abnormality has been diagnosed in laparoscopically directed biopsies will reveal the natural history of this lesion[17].

Does malignant change occur with any frequency in benign ovarian epithelial cystadenomas? Can such neoplasms be considered important precursors of malignancy? It has been said that the evidence for overt adenocarcinomas arising in benign ovarian tumors is "unimpeachable"[18], but, in reality, any views expressed on this topic must be largely anecdotal and highly subjective. It is certainly true that the peak age incidence of women with benign epithelial ovarian tumors is lower than that of patients with malignant epithelial neoplasms[19,20], but this observation is, in itself, no proof of progression from benign to malignant lesions and is more than counterbalanced by the rarity with which focal adenocarcinomatous change is seen in serous cystadenomas. Focal mural nodules of carcinoma have been noted in mucinous cystadenomas[21,22] but are, nevertheless, extremely uncommon. It can be argued that the relatively rapid growth of a malignant, as opposed to benign, neoplasm will very rapidly lead to obliteration by an adenocarcinoma of any preceding benign cystadenoma, but such a claim can be either confirmed or refuted. It should be noted in this respect that the presence within a

malignant ovarian neoplasm of apparently benign epithelium does not, in itself, necessarily indicate that the carcinoma has evolved from a previously present cystadenoma; areas of apparently benign epithelium occur with moderate frequency in metastatic carcinomas of the ovary[23].

Although focal malignant change is encountered extremely infrequently in mucinous or serous cystadenomas, it is significantly less unusual to find an adenocarcinoma either clearly arising in, or showing a transition from, a focus of ovarian endometriosis. Quite often the ovarian endometriosis in such cases is, in fact, an endometriotic cyst; there is much to suggest that many such cysts are, in reality, endometrioid cystadenomas rather than true foci of endometriosis [24]. The true incidence of malignant change in ovarian endometriosis is difficult to assess; quite often, the diagnosis of adenocarcinoma arising in ovarian endometriosis is based on evidence of endometriosis in the contralateral ovary or elsewhere in the pelvis. Nevertheless, it has been estimated that 15-20% of ovarian endometrioid adenocarcinomas arise in this fashion[25]. This, if true, would suggest that,endometrioid cystadenomas are a significant precursor of adenocarcinoma, but it must be borne in mind that haemosiderin deposition is common in endometriotic cysts, that iron is a well recognized carcinogen, and that, therefore, endometrioid cystadenomas cannot

be taken as typical benign neoplasms in terms of their malignant potential.

Early malignant change is clearly recognised as occurring in ovarian epithelial tumors of borderline malignancy. Overt foci of malignant change in serous borderline tumors are distinctly uncommon in conventional terms, but focal, limited, nondestructive invasion of tumor stroma by epithelial cells has recently been described in a subset of such neoplasms[26,27]. The invasion takes the form of isolated cells, nests of neoplastic cells, or papillary clusters of cells; in some cases, lymphatic invasion is also seen. These tumors appear to behave in exactly the same manner as do serous borderline tumors without focal stromal invasion; therefore, although such neoplasms are technically malignant, they can still be treated as borderline tumors rather than as adenocarcinomas. Whether tumors showing this pattern of invasion should be regarded as examples of early malignant change is a moot point.

**Conclusion:**

There is no doubt that focal evolution into an obvious adenocarcinoma occurs much more commonly in mucinous tumors of borderline malignancy than in their serous counterparts. It is relatively common to encounter a mucinous neoplasm that shows a borderline pattern in some areas and a clearly malignant pattern in others, whilst, by no means infrequently, mucinous neoplasms show a melange of benign, borderline, and malignant patterns[28]. Mucinous tumors showing definite, albeit focal, adenocarcinomatous change are considered to be genuine adenocarcinomas, but we do not know the natural history of such neoplasms. Is the prognosis for patients with such tumors better than for a woman with a conventional Stage IA well differentiated mucinous adenocarcinoma? Information about this point is not available and is unlikely to become available in the foreseeable future until, and unless, a multicenter study with central pathology review is instigated.

It is clear, from consideration of the above reviews, that our knowledge about the morphology of early malignant change in the ovary is very inadequate. We do not have any real knowledge of the malignant potential of benign cystadeomas, and we do not know the natural history of tumors characterized by focal malignant change in neoplasms of borderline malignancy. In addition, we do not know if the lesion classed as ovarian intraepithelial neoplasia has potential for progression to an invasive neoplasm. It is difficult to see how any of these lacunae in our knowledge can be repaired by purely morphological techniques, and it is probable that further progress in this field will come only from a more sophisticated approach involving the study, within ovarian epithelial cells, of changes such as altered glycoprotein synthesis[29,30], abnormalities in the expression of oncogenes, and tumor suppression genes or changes in genetic make-up. However diagnosis of early malignant change in ovary will surely help to define better treatment planed and survive of the patient.

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